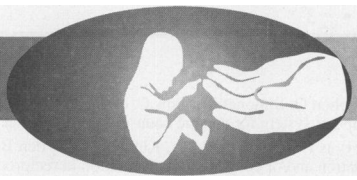

Prenatal Diagnosis and Significance of Fetal Infections

ALESSANDRO GHIDINI, MD, *and* LAUREN LYNCH, MD, *New York, New York*

Viruses like rubella, cytomegalovirus, varicella-zoster virus and parasites like *Toxoplasma gondii* can be transmitted from a pregnant woman to her fetus and can affect fetal development. Several factors determine the likelihood of fetal infection and the risk of consequences for the fetus, such as the timing of transmission during gestation or the immunologic status of the mother. No single diagnostic modality can be applied to all infections. Knowledge of the diagnostic methods available is essential for accurate counseling and treatment of affected pregnant women.

(Ghidini A, Lynch L: Prenatal diagnosis and significance of fetal infections, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:366-373)

Maternal infection can lead to fetal infection by hematologic spread to the placenta and hence to the fetus. As a consequence of this route of infection, the infection can be limited to the placenta or both placenta and fetus can be infected. The timing and extent of fetal infection following maternal infection can vary, depending on the type of infection, the gestational age at infection, and the immunologic status of the mother. Evidence of fetal infection relies on the identification of the organism or detection of its antigens or genome in fetal compartments (amniotic fluid, fetal blood, or ascitic fluid) or the detection of specific immunoglobulin (Ig) M antibodies targeted to the offending organism in the fetal blood or amniotic fluid. Identifying an infectious agent can sometimes take weeks, however. The production of specific IgM antibodies depends on the maturity of the fetal immune system and the immunogenicity of the specific infectious agent. Therefore, the detection of specific IgM antibodies is reliable evidence of fetal infection, but their absence does not rule it out. Nonspecific evidence of fetal infection can also be obtained from fetal blood sampling—elevated total IgM antibodies, thrombocytopenia, eosinophilia, and elevated liver enzyme levels—and although not diagnostic, it increases the likelihood of fetal involvement in the presence of a documented recent maternal infection.

The most common pathogen transmitted in utero is cytomegalovirus (CMV), with an incidence of about 1% to 2% of pregnancies. *Toxoplasma gondii* infects about 4 of 1,000 pregnant women per year, causing congenital infection in 3,700 of the 3.7 million infants born a year in the United States. Every year 1,500 cases of varicella-zoster virus infection during pregnancy are reported in this country. The occurrence during pregnancy of rubella virus infection, once an important causative agent of congenital malformations, has substantially decreased, thanks to a general program of vaccination, but 21 infants were born with the rubella syndrome in southern California during 1990.[1] The incidence of parvovirus B19 infection in pregnancy is unknown, but it is probably rare.[2] Each year in the United States, about 6,000 pregnant women infected with the human immunodeficiency virus type 1 (HIV-1) deliver, and although the virus is not teratogenic, infected newborns succumb within a few years of life to opportunistic infections. For many of the specific infections discussed in this article, few data are available in the literature, and specific recommendations cannot be made.

Cytomegalovirus Infection

Like other herpesviruses, CMV can cause primary and recurrent infections. About 50% to 85% of women of reproductive age show serologic evidence of a previous CMV infection. The attack rate among susceptible women is about 2% per year among women at a higher socioeconomic level, compared with a 6% annual attack rate among women of lower income.[3]

Fetal CMV infection can follow either a primary or reactivated maternal infection. From 30% to 40% of pregnant women with primary CMV infection transmit the virus to their fetuses; 10% of these fetuses will be symptomatic at birth, and the infection will result in neonatal death or mental retardation and neurologic problems in most of the survivors. Of the 90% asymptomatic infected fetuses, 5% to 15% will have long-term neurologic sequelae develop later in childhood, usually in the form of

From the Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Maternal-Fetal Medicine, Mount Sinai School of Medicine, New York, New York.

Reprints are not available.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV-1 = human immunodeficiency virus type 1
Ig = immunoglobulin
PCR = polymerase chain reaction

a mild to profound hearing loss. Gestational age at the time of maternal infection does not affect the transmission rate, but it seems to influence the severity of the infection, with most symptomatic infants being born to women who acquire CMV infection in early gestation.[3] Among women with immunity to CMV, about 0.5% to 1% have a recurrent infection during pregnancy. Preexisting maternal antibodies to CMV seem to protect the fetus, however, and lessen the incidence and severity of the manifestations of congenital CMV infection.

A recent study has compared the outcomes of 125 CMV-infected infants born to women who acquired primary infection during pregnancy with those of 64 CMV-infected infants born to women with recurrent infection during pregnancy.[4] At birth, 18% of the infants in the primary-infection group had symptomatic CMV infection compared with none in the recurrent-infection group. After a mean follow-up of 4.7 years, one or more sequelae were seen among initially asymptomatic infants in 25% of the primary-infection group compared with 8% of the recurrent-infection group ($P = .003$), including mental retardation in 13% versus 0% and hearing loss in 23% versus 5%, respectively.

The diagnosis of in utero infection after a documented maternal infection requires a combination of ultrasonography and invasive procedures, such as amniocentesis and fetal blood sampling. By compiling the series published in the literature,[5-7] we found a total of 24 cases that have been evaluated after primary maternal CMV infection and after routine serologic screening. Fetal infection was documented in 11 cases and excluded in the rest (Table 1). In these patients, the detection of CMV early antigens and culture of the virus from amniotic fluid were the most reliable diagnostic tests. A fetal blood specimen obtained by cordocentesis can be tested for specific IgM antibodies and for nonspecific signs of in utero infection, such as anemia, thrombocytopenia, elevated leukocyte counts or total IgM levels, or abnormal liver function test results. Specific fetal IgM antibodies were present in only five (63%) of eight fetuses, and fetal blood culture grew CMV in one (13%) of the eight cases in which fetal blood sampling was done. On ultrasound examination, intrauterine CMV infection may present as ascites or generalized hydrops, ventriculomegaly, intracranial calcifications, increased bowel echodensity, and growth retardation.[5,8] All fetuses at risk with abnormal sonographic findings have been found to be infected.[5,6,8-10] The converse is not true, however: the absence of abnormal sonographic findings does not rule out infection in a fetus.

Pregnant women with documented seroconversion to CMV should be offered amniocentesis for viral identification. Fetal blood sampling can be offered if other potential prognostic indicators—total IgM antibody titers, hematologic indices, and liver function tests—are desired. In the absence of ultrasonographic findings, we are unable to predict which fetuses will be clinically affected. The CMV genome can be detected by hybridization or polymerase chain reaction (PCR),[11] but these techniques are currently used only on an investigational basis.

Ganciclovir, with or without CMV-hyperimmune globulin, has been used with success in the treatment of adults and neonates with CMV infection.[12] It may decrease viral shedding and reduce the risk of organ damage in cases of in utero infection. Before this is attempted, larger trials evaluating the clinical efficacy and safety in newborns will be necessary.

Toxoplasmosis Infection

Toxoplasma gondii is a protozoan transmitted by oocysts in cat feces, infected meat eaten raw or inadequately cooked, and unwashed vegetables and fruit. Acute infection is asymptomatic in almost 90% of patients. After host cell invasion, *T gondii* forms cysts in all tissues (most commonly in the brain, skeletal muscles,

TABLE 1.—*Prenatal Diagnosis of Cytomegalovirus (CMV) Infection in 11 Infected Fetuses*

Fetus	Source	Early Antigen Detected in Amniotic Fluid	CMV in Culture: Amniotic Fluid	CMV in Culture: Fetal Blood	Ultrasonographic Findings	Fetal CMV IgM	Aspecific Findings	Outcome
1	Lynch et al, 1991[5]	Yes	Yes	Yes	Normal	No	Yes	Pregnancy terminated
2	Hohlfeld et al, 1991[6]	Yes	Yes	No	Ascites	Yes	Yes	Pregnancy terminated
3		Yes	Yes	No	Normal	Yes	Yes	Pregnancy terminated
4		Yes	Yes	No	Normal	Yes	Yes	Neonatal infection
5		Yes	Yes	No	Normal	Yes	Yes	Subclinical infection
6		Yes	Yes	No	Normal	Yes	Yes	Pregnancy terminated
7		Yes	Yes	No	Normal	No	Yes	Subclinical infection
8		Yes	Yes	No	Normal	No	No	Subclinical infection
9	Skvorc-Ranko et al, 1991[7]	NA	Yes	NA	NA	NA	NA	Subclinical infection
10		NA	Yes	NA	NA	NA	NA	Subclinical infection
11		NA	Yes	NA	NA	NA	NA	Subclinical infection

NA = not available

and heart), where it persists for the life of the host. Reactivations with parasitemia are possible in immunocompromised patients.[13] About 40% of pregnant women in the United States are immune to toxoplasmosis.[14] About 4 of 1,000 susceptible pregnant women will acquire toxoplasmosis during the nine months of gestation. Because 40% of such women, if not treated, will give birth to infected infants, the annual incidence of congenital infection is 1 to 2 per 1,000.

A diagnosis of recent *T gondii* infection can be made in the presence of documented seroconversion from a negative to a positive titer; specific IgM antibodies, even though there are substantial individual variations in response to infection (in many cases immunocapture methods can detect IgM antibodies more than a year after the acute infection)[15]; or a fourfold increase in specific IgG titer when sampling is done at three-week intervals in the absence of treatment. A serologic diagnosis requires a careful interpretation of the results because some tests have different sensitivities at various stages of infection. It is important to rely on a reference laboratory where several tests can be done in parallel with evaluations of previous specimens. There is as yet no consensus on whether routine testing for toxoplasmosis in pregnancy is cost-effective.

Vertical transmission occurs only during maternal parasitemia, hence during acute infections or reactivated latent infections in immunocompromised persons. Infection of the placenta is an obligatory step for maternal-to-fetal transmission. Once the placenta becomes infected, it remains so for the duration of the pregnancy. The delay between maternal and fetal infection varies from less than 4 weeks to more than 16 weeks.[16] The transplacental passage increases with the gestational age: only 1.2% of fetuses are infected when maternal infection occurs around the time of conception, whereas the incidence of fetal infection increases to 4.5% if the mother was infected at 6 to 16 weeks, 17.3% if infected at 17 to 20 weeks, and 28.9% if infected after midgestation.[17] The incidence of severe fetal infection, however, decreases from about 75% during first-trimester maternal infection to almost 0% for transmission during the third trimester.[18]

Overall, 20% to 30% of untreated infected neonates are symptomatic at birth (convulsions, spasticity, hypotonia, chorioretinitis, encephalitis, hydrocephalus, microcephaly). Among asymptomatic neonates, chorioretinitis will develop in almost all untreated persons by adulthood, and about 50% will have severe visual impairment.[19] Antibiotic treatment for a year after birth is currently recommended, but it has not been determined whether treatment improves the long-term outcome.[19] The visualization of intracranial calcifications or hydrocephalus by ultrasonogram is not only diagnostic of fetal infection but also suggestive of severe fetal involvement.

As soon as the diagnosis of recently acquired toxoplasmosis is made or suspected in a pregnant woman who desires the continuation of her pregnancy, antibiotic treatment should be started to reduce the probability of the transmission of parasites to the fetus. At the same time, further evaluation can be carried out to determine whether the fetus is already infected. A combination of amniocentesis, ultrasonography, and fetal blood sampling can lead to a correct diagnosis of fetal infection in about 92% of cases.[20] The sensitivity and specificity of the different diagnostic tests are shown in Table 2. With the absence of false-positive results, fetal blood sampling is diagnostic of congenital toxoplasmosis when specific signs of infection, such as *T gondii* IgM titers or parasites, are detected. Amniocentesis is diagnostic of fetal infection if the parasite is identified in amniotic fluid. The identification of *T gondii* by mouse inoculation requires three to six weeks; fibroblast cell culture requires less than a week, but it is less sensitive.[21] Preliminary data show that PCR amplification for detecting the *T gondii* genome is the most sensitive and specific test,[22,23] but its use is currently limited to research centers.

TABLE 2.—*Accuracy of Diagnostic Tests for Congenital Toxoplasmosis**

Test	Sensitivity, %	Specificity, %
Fetal blood sampling		
Identification of parasites in fetal blood	64	100
Elevated γ-glutamyltransferase	57	97
Total IgM	52	97
Elevated leukocyte count	38	97
Low platelet count	28	98
Specific IgM antibodies	21	100
Elevated eosinophil count	19	94
Elevated lactate dehydrogenase	17	98
Amniocentesis	52	100
Ultrasonogram	45	99.8

*Modified from Daffos et al.[20]

The treatment of a woman during pregnancy substantially reduces the likelihood of fetal infection. Spiramycin has few maternal side effects, no teratogenic action, but scarce transplacental passage, so that its therapeutic effect consists mainly of preventing the parasites from crossing the placenta. A more aggressive antibiotic treatment with sulfonamides and pyrimethamine can alternatively be used, and their use has been recommended in cases of documented vertical transmission to decrease the severity of fetal infection. In a large series from France, 16 (14%) of 116 untreated women had infants severely affected at birth, compared with 3 (4%) of 79 women treated with a combination of sulfonamides-pyrimethamine and spiramycin.[24] In a more recent series, the incidence of the presence of specific IgM antibodies and of clinical infection was considerably lower among newborns whose mothers were treated with a combination of pyrimethamine-sulfadiazine and spiramycin, compared with newborns whose mothers received spiramycin alone.[25]

Varicella-Herpes Zoster Virus Infection

The varicella-zoster virus is a member of the herpesvirus family. The incubation period is 15 ± 5 days, and

it is contagious between two days before and five days after the outbreak of the rash. About 95% of adults are immune. Subclinical infection is uncommon. The incidence of varicella infection in pregnancy is about 1 in 2,000 pregnancies, whereas that of herpes zoster is 1 in 10,000. Evidence of fetal infection following maternal varicella is seen in 24% of cases,[26] but it is rare after maternal herpes zoster, probably because the latter is rarely associated with viremia.

A well-recognized "congenital varicella syndrome" (also called varicella embryopathy) has been described in a small proportion of infected fetuses. Pooling of the data from several prospective studies indicates that the risk of the congenital varicella syndrome is 1.8% (3/167) if maternal infection occurs during the first trimester and less than 1% if it occurs after the first trimester.[26-30] In all, 36 cases of the syndrome have been reported.[31-38] Anomalies included cicatricial skin lesions (usually conforming to a dermatomal distribution), limb abnormalities (hypoplasia, contractures), ocular abnormalities (chorioretinitis, microphthalmia, cataracts), and neurologic abnormalities (including peripheral, central, and autonomic nervous systems: paralysis, seizures, microcephaly, hydrocephaly). It has been suggested that the fetal abnormalities are not due to direct damage from the varicella, but to in utero reactivation of the infection leading to fetal herpes zoster.[32] A latency period of at least five weeks between maternal infection and fetal abnormalities has been documented in cases detected in utero by ultrasonography.[36] About a third of infants with the congenital varicella syndrome die in the neonatal period, and most survivors have substantial sequelae.[39]

The prenatal diagnosis of the congenital varicella syndrome is challenging. Chorionic villus sampling and the PCR technique have been used in two cases to document placental infection, but neither of the two fetuses appeared to be infected.[40] Ultrasonography has shown abnormalities in eight of nine fetuses later diagnosed with the fetal varicella syndrome (Table 3)[31,33-36,41]; the most common findings were polyhydramnios, liver hyperechogenicities, and fetal hydrops. The detection of viral DNA in amniotic fluid by the PCR technique may prove to be a sensitive indicator of fetal infection, but it awaits further investigation.

Fetal blood sampling has limited application because viremia is present for a limited time, and specific fetal IgM is absent in more than half of infected newborns. One case of successful prenatal diagnosis by fetal blood sampling has been reported: the mother had been infected at 20 weeks, and fetal blood sampling at 32 weeks revealed specific IgM and high total IgM titers.[31]

Varicella-zoster immune globulin prevents clinical varicella when given to susceptible persons within 96 hours of exposure. It should be given to pregnant women who have had exposure to the virus who are without evidence of or with unknown immunity and neonates whose mothers had varicella within a few days of delivery. Neonatal mortality in this situation can be high because synthesis and the transplacental passage of specific maternal IgG have not had time to occur. Acyclovir treatment should be considered when delivery is anticipated within a few days of maternal infection. The drug crosses the placenta, may inhibit in utero viral replication, and may lessen the severity of postnatal disease. There is no evidence, however, that varicella-zoster immune globulin, acyclovir, or interferon treatment can alter the course of intrauterine infection or prevent fetal infection.

Rubella Infection

Rubella is an RNA virus without a serologic relationship to other known viruses that can affect humans. Infection is asymptomatic in 25% to 50% of cases. In developed countries, only 5% to 20% of women of reproductive age are susceptible to the virus. Despite a program of rubella screening and vaccination in women, the number of reported cases of rubella infection in the general and in the obstetric populations of the United States has recently increased.[1,42] Past rubella infection can be diagnosed by the detection of specific IgG antibodies, whose presence correlates with protective immunity. Recent infection is documented by the presence of specific IgM antibodies that can be detected shortly after the onset of illness; their levels peak at seven to ten days, and they persist as long as four weeks after the appearance of the rash.[43]

TABLE 3.—*Sonographic Findings in Fetuses With the Congenital Varicella Syndrome*

Fetus	Source	Gestational Age, wk: At Exposure	Gestational Age, wk: At Ultrasonogram	Sonographic Findings	Outcome
1	Alexander, 1979[41]	16	31	Polyhydramnios	Neonatal death
2	Cuthbertson et al, 1987[31]	20	32	Polyhydramnios, hydrocephaly	Neonatal death
3	Harding and Baumer, 1988[33]	14	17	Normal	Neonatal death
4	Scharf et al, 1990[34]	14	28	Polyhydramnios, hydrocephaly, clubfeet	Neonatal death
5	Byrne et al, 1990[35]	15	30	Liver hyperechogenicity, polyhydramnios	Alive
6	Pretorius et al, 1992[36]	16	35	Polyhydramnios	Neonatal death
7		16	24	Polyhydramnios, hydrops, liver hyperechogenicity	Neonatal death
8		13	32	Polyhydramnios, liver hyperechogenicity	Neonatal death
9		14	19	Hydrops, arthrogryposis, liver hyperechogenicity	Neonatal death

Subclinical reinfection is possible, both after natural infection and after vaccination. It is diagnosed serologically by a notable (greater than fourfold) increase in antibody concentration or the detection of IgM antibodies in a person with known rubella antibodies.[44] The incidence of vertical transmission (fetal infection rate) declines from 90% during the first trimester to 25% at the end of the second trimester, and then rises again to 95% to 100% during the last month of pregnancy.[45,46] During the first trimester, the risk of fetal infection is nonexistent when the maternal rash appears within 12 days from the last menstrual period, increases to 31% when the rash occurs 12 to 21 days from the last menstrual period, and is 100% in cases of maternal infection 3 to 6 weeks from the last period.[47]

The risk of fetal damage in cases of fetal infection decreases from almost 100% during the first trimester to 35% during the early second trimester (Table 4).[45,47-49] No severe damage has been observed after the 17th week of pregnancy, with these children presenting with only subclinical forms of congenital rubella.[49] Long-term studies on these cases are not available. No cases of fetal damage after maternal vaccination in pregnancy have been reported, even though theoretic concerns still contraindicate rubella vaccination during pregnancy.

The most commonly described anomalies associated with the congenital rubella syndrome are ophthalmologic (cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (patent ductus arteriosus, pulmonary artery stenosis, atrial or ventricular septal defects), and neurologic (sensorineural deafness, microcephaly, mental retardation). In addition, most affected infants have retarded growth and nonspecific findings of congenital infection (hepatosplenomegaly, thrombocytopenia). Milder cases may go unrecognized for months or even years after birth.

The termination of pregnancy should be offered in cases of maternal infection at between 3 and 10 weeks' gestation. The rate of fetal infection and birth defects is lower from 11 to 18 weeks, and the option of a prenatal diagnosis should be offered to these patients. This has been accomplished by the detection of specific IgM in fetal blood. Fetal IgM can be synthesized from the 12th week of gestation, but is consistently found only after the 22nd week in cases of rubella infection.[50] The overall sensitivity of prenatal diagnosis in the largest series available (n = 119) has been 98% (59/60), with specificity of 100% (59/59).[50] The only incorrect diagnosis (false-negative) was thought to be due to sampling too early during pregnancy (20 weeks). The virus can also be isolated from the amniotic fluid and grown in primary cell cultures,[7,51-53] but the method is insensitive and time consuming (up to six weeks). Alternatively, viral RNA can be detected by in situ hybridization or PCR,[54-56] but the accuracy of these newer techniques is unknown. Because all infected fetuses produce IgM, this method cannot be used to differentiate fetuses who are clinically affected from those who are unaffected. Given the rarity of fetal sequelae when infection occurs after midgestation, terminating the pregnancy or doing invasive diagnostic studies to detect fetal infection is not recommended.

Immune globulin therapy after exposure to rubella early in pregnancy does not prevent fetal infection or teratogenic effects. Its use can be considered only when a pregnant woman with exposure to rubella would not consider terminating the pregnancy under any circumstances.[45] No antiviral treatment is yet available or tested.

Human Parvovirus B19 Infection

The most common clinical manifestations of B19 infection are erythema infectiosum, arthralgias, or arthritis, with low-grade fever and flulike symptoms. Parvovirus B19 infection can be entirely asymptomatic in about 20% of women. It is common in childhood, and nearly 50% of women at childbearing age are immune.[57] The attack rate among susceptible household contacts is about 50%, and during school outbreaks, the transmission of infection to susceptible teachers is about 20%.[58]

The primary sites for B19 replication are the erythroid progenitor cells in the bone marrow. The infection is lytic in nature, leading to erythrocytes failing to mature. The

TABLE 4.—*Fetal Infection Rates After Confirmed Maternal Rubella Infection**

Gestational Age, wk	*Fetal Infection, No. Infected/No. Exposed (%)*	*Rubella-Associated Defects/ Seropositive Infants, No./No. (%)*	*Overall Risk†*
2-3	4/13 (31)	NA	NA
4-6	10/10 (100)	11/11 (100)	100
7-10	9/9 (100)	24/29 (83)	83
11-12	8/13 (62)	20/25 (80)	55
13-14	16/25 (64)	16/31 (52)	33
15-16	24/46 (52)	17/38 (45)	23
17-20	13/33 (39)	2/33 (6)	2
21-23	6/35 (17)	0/16 (0)	0
24-30	19/63 (30)	(0)	0
31-36	15/25 (60)	(0)	0
>36	8/8 (100)	(0)	0

NA = not available

*From Miller et al,[45] Enders et al,[47] Munro et al,[48] and Grillner et al.[49]
†The overall risk was calculated as follows: % seropositive fetuses with defects × % infants infected.

aplastic event lasts seven to ten days, after which time reticulocytes appear; the bone marrow fully recovers within about three weeks. Adults with normal hematopoiesis tolerate this transient red cell aplasia with a minimal decrease in hemoglobin; however, anemia may develop in cases of infection when there is rapid erythrocyte turnover (as in fetuses).

The mainstay of the diagnosis of B19 infection in pregnant women with exposure to parvovirus or with symptoms of infection is the use of serologic tests. B19-specific IgM antibodies appear within 3 days after the illness begins, but persist for only 30 to 60 days; specific IgG antibodies appear after a week and can be used to document recent infection if both acute and convalescent sera are tested simultaneously and display a substantial rise in antibody titers. The B19 virus cannot be cultured on traditional tissue culture media. In the fetus, viral particles can be identified in fetal tissues (ascitic fluid),[59] or viral DNA can be detected by either in situ hybridization or Southern blot techniques.[59-61] Parvovirus B19 DNA probes are most useful during the acute viremic phase of the infection and may show normal findings after symptoms resolve.[62]

Recently, DNA amplification by PCR has been used that allowed the detection of viral DNA in amniotic fluid,[63] but this technique is currently available in only a few research laboratories. Specific fetal IgM antibodies can also be detected in amniotic fluid or umbilical cord blood.[53] Amniocentesis and fetal blood sampling are indicated in the presence of hydrops. Amniocentesis is not yet recommended in all cases of maternal B19 infection because of the lack of a laboratory willing to do viral identification by the PCR technique in amniotic fluid.

The transplacental transmission rate of B19 has been estimated to be 33%.[2] It has been estimated that the risk of fetal death due to B19 infection is about 9%.[2] Preliminary data from a prospective cohort study of about 200 women with serologic evidence of acute B19 infection indicate that there is a 2% to 3% increase in fetal deaths among infected women compared with controls.[64]

Parvovirus B19 infection can jeopardize a fetus at any gestational age. Severe anemia and hydrops precede fetal death in most cases.[61] When present, hydrops generally occurs 3 to 5 weeks after symptomatic infection in the mother, but it has been reported as long as 12 weeks later.[2,61] Therefore, once maternal infection has been documented, serial sonographic examinations every one to two weeks are indicated to detect early signs of hydrops. Surveillance should be started as early as possible because hydrops due to B19 infection has been seen as early as 11 weeks' gestation.[2] Some fetuses can become hydropic without evidence of anemia: because viral particles have been recovered from the myocardium, in these cases hydrops has been thought to be due to cardiomyopathy.[63,65,66]

Although most fetuses with hydrops die in utero if not transfused, cases of transient hydrops and survival without therapeutic intervention have been reported.[62,67,68] It is unclear whether in utero transfusion improves fetal outcome. Infants who survive the severe anemia with or without in utero transfusion appear to develop normally. There is no conclusive evidence that B19 infection is associated with anatomic abnormalities. The efficacy of maternal prophylactic immune globulin administration after exposure has not been determined yet, and its use is not recommended at this time. A vaccine is not available, but its implementation should be made easier by the antigenic stability of B19 virus.

Human Immunodeficiency Virus Type 1 Infection in Pregnancy

About 6,000 HIV-1-positive women give birth in the United States during a 12-month period.[69] Modes of infection in women include injection drug use (52%), heterosexual transmission (33%), and exposure to blood products, but a substantial proportion of infected women do not acknowledge risky behaviors. Pregnancy does not seem to be associated with an accelerated progression of HIV-1 disease.[70]

Data from several prospective studies show that vertical transmission rates range between 13% and 30% of cases.[71-73] The risk of infection appears to be greatest for infants born to women with advanced infection (such as those with the acquired immunodeficiency syndrome [AIDS], with $CD4^+$ counts during the third trimester below 700×10^6 per liter [700 per μl], or with evidence of p24 antigen in the blood) and for those delivered before 34 weeks of gestation.[71] Even though fetal infection during the second trimester has been documented,[74,75] recent findings strongly suggest that in a significant proportion of cases, HIV-1 is transmitted from mother to infant at the time of delivery: indeed, for twins born to HIV-infected mothers, the first child delivered, either vaginally or by cesarean section, is more likely to be HIV-infected than the second one.[76] If HIV-1 were transmitted across the placenta earlier in pregnancy, birth order should make no difference in the infection rate. Episiotomy, the application of scalp electrodes, and instrumental deliveries were associated with an increased risk of transmission only in centers where these procedures were not routinely used.

Prenatal diagnosis is not recommended as invasive procedures like fetal blood sampling may theoretically introduce the virus into a previously uninfected fetus. The magnitude of this risk is unknown. Furthermore, a fetus may become infected anytime after prenatal diagnosis because maternal viremia persists. Fetal HIV-1 infection does not seem to be associated with a substantially increased incidence of intrauterine growth retardation, prematurity, microcephaly, or dysmorphism once other confounding variables are taken into account.[71,77,78]

The mainstay of the treatment of nonpregnant women with AIDS, AIDS-related complex, or $CD4^+$ cell counts of less than 200×10^6 per liter rests on antiretroviral therapy with zidovudine and *Pneumocystis carinii* pneumonia prophylaxis with the combination drug trimethoprim and sulfamethoxazole.

Because of the lack of solid data on the fetal side effects and toxicities, the Public Health Service has avoided

recommending therapies in pregnancy, but as there are no adverse fetal effects known to outweigh the maternal benefits of these therapies, they should not be withheld during pregnancy.[79] Most obstetricians offer zidovudine treatment to pregnant women in advanced stages of disease, avoiding its use during the first trimester because of possible teratogenic risks.

REFERENCES

1. Lee SH, Ewert DP, Frederick PD, Mascola L: Resurgence of congenital rubella syndrome in the 1990s. JAMA 1992; 267:2616-2620

2. Public Health Laboratory Service Working Party on Fifth Disease: Prospective study of human parvovirus (B19) infection in pregnancy. BMJ 1990; 300:1166-1170

3. Stagno S, Pass RF, Cloud G, et al: Primary cytomegalovirus infection in pregnancy: Incidence, transmission to fetus, and clinical outcome. JAMA 1986; 256:1904-1908

4. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA: The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992; 326:663-667

5. Lynch L, Daffos F, Emanuel D, et al: Prenatal diagnosis of fetal cytomegalovirus infection. Am J Obstet Gynecol 1991; 165:714-718

6. Hohlfeld P, Vial Y, Maillard-Brignon C, Vaudaux B, Fawer CL: Cytomegalovirus fetal infection: Prenatal diagnosis. Obstet Gynecol 1991; 78:615-618

7. Skvorc-Ranko R, Lavoie H, St Denis P, et al: Intrauterine diagnosis of cytomegalovirus and rubella infections by amniocentesis. Can Med Assoc J 1991; 145:649-654

8. Pletcher BA, Williams MK, Multivor RA, Barth D, Linder C, Rawlinson K: Intrauterine cytomegalovirus infection presenting as fetal meconium peritonitis. Obstet Gynecol 1991; 78:903-905

9. Mittelmann-Handwerker S, Pardes JG, Post RC, et al: Fetal ventriculomegaly and brain atrophy in a woman with intrauterine cytomegalovirus infection—A case report. J Reprod Med 1986; 31:1061-1064

10. Binder ND, Buckmaster JW, Benda GI: Outcome for fetus with ascites and cytomegalovirus infection. Pediatrics 1988; 82:100-103

11. Einsele H, Ehninger G, Steidle M, et al: Polymerase chain reaction to evaluate antiviral therapy for cytomegalovirus disease. Lancet 1991; 338:1170-1172

12. Havard-Fan P, Nahata MC, Brady MT: Ganciclovir—A review of pharmacology, therapeutic efficacy and potential use for treatment of congenital cytomegalovirus infections. J Clin Pharm Ther 1989; 14:329-340

13. Desmonts G, Couvreur J, Thulliez P: Toxoplasmose congénitale: Cinq cas de transmission à l'enfant d'une infection, maternelle antérieure à la grossesse. Presse Med 1990; 19:1445-1449 (Eng Abstr)

14. Sever JL, Ellenberg JH, Ley AC, et al: Toxoplasmosis: Maternal and pediatric findings in 23,000 pregnancies. Pediatrics 1988; 82:181-192

15. Ades AE: Evaluating the sensitivity and predictive value of tests of recent infection: Toxoplasmosis in pregnancy. Epidemiol Infect 1991; 107:527-535

16. Remington JS, Desmonts G: Toxoplasmosis, chap 4, *In* Remington JS, Klein JO (Eds): Infectious Diseases of the Fetus and Newborn Infant, 3rd Ed. Philadelphia, Pa, WB Saunders, 1990, pp 89-195

17. Hohlfeld P, Daffos F, Thulliez P, et al: Fetal toxoplasmosis: Outcome of pregnancy and infant follow-up after in utero treatment. J Pediatr 1989; 115:765-769

18. Desmonts G, Couvreur J: Toxoplasmose congénitale: Etude prospective de l'issue de la grossesse chez 542 femmes atteintes de toxoplasmose acquise en cours de gestation. Ann Pediatr (Paris) 1984; 31:805-809

19. McLeod R, Remington JS: Toxoplasmosis, *In* Behrman RE, Kliegman RM, Nelson WE, Vaughan VC (Eds): Nelson Textbook of Pediatrics, 14th edition. Philadelphia, Pa, WB Saunders, 1992, pp 883-892

20. Daffos F, Forestier F, Capella-Pavlosky M, et al: Prenatal management of 746 pregnancies at risk for congenital toxoplasmosis. N Engl J Med 1988; 318:271-275

21. Derouin F, Thulliez P, Candolfi E, Daffos F, Forestier F: Early prenatal diagnosis of congenital toxoplasmosis using amniotic fluid samples and tissue culture. Eur J Clin Microbiol Infect Dis 1988; 7:423-425

22. Grover CM, Thulliez P, Remington JS, Boothroyd JC: Rapid prenatal diagnosis of congenital *Toxoplasma* infection by using polymerase chain reaction and amniotic fluid. J Clin Microbiol 1990; 28:2297-2301

23. Cazenave J, Forestier F, Bessieres MH, Broussin B, Begueret J: Contribution of a new PCR assay to the prenatal diagnosis of congenital toxoplasmosis. Prenat Diagn 1992; 12:119-127

24. Couvreur J, Desmonts G, Tournier G, Szusterkac M: Etude d'une série homogène de 210 cas de toxoplasmose congénitale chez des nourrissons âgés de 0 à 11 mois et dépistés de façon prospective. Ann Pediatr (Paris) 1984; 31:815-819

25. Couvreur J, Thulliez P, Daffos F, et al: Foetopathie toxoplasmique—Traitement in utero par l'association pyriméthamine-sulfamides. Arch Fr Pediatr 1991; 48:397-403 (Eng Abstr)

26. Paryani SG, Arvin AM: Intrauterine infection with varicella-zoster virus after maternal varicella. N Engl J Med 1986; 314:1542-1546

27. Siegel M: Congenital malformations following chickenpox, measles, mumps, and hepatitis: Results of a cohort study. JAMA 1973; 226:1521-1524

28. Enders G: Varicella-zoster virus infection in pregnancy. Prog Med Virol 1984; 29:166-196

29. Preblud S, Cochi S, Orenstein W: Varicella-zoster infection in pregnancy. N Engl J Med 1986; 315:1416-1417

30. Balducci J, Rodis JF, Rosengren S, Vintzileos AM, Spivey G, Vosseller C: Pregnancy outcome following first trimester varicella infection. Obstet Gynecol 1992; 79:5-6

31. Cuthbertson G, Weiner CP, Giller RH, Grose C: Prenatal diagnosis of second trimester congenital varicella syndrome by virus-specific immunoglobulin M. J Pediatr 1987; 111:592-595

32. Higa K, Don K, Manahe H: Varicella-zoster virus infections during pregnancy—Hypothesis concerning the mechanisms of congenital malformations. Obstet Gynecol 1987; 69:214-222

33. Harding B, Baumer JA: Congenital varicella-zoster: A serologically proven case with necrotizing encephalitis and malformation. Acta Neuropathol 1988; 76:311-315

34. Scharf A, Scherr O, Enders G, et al: Virus detection in the fetal tissue of a premature delivery with congenital varicella syndrome: A case report. J Perinat Med 1990; 18:317-322

35. Byrne JLB, Ward K, Kochenour NK, Dolcourt JL: Prenatal sonographic diagnosis of fetal varicella syndrome. Am J Hum Genet 1990 (Abstr); 47:A270

36. Pretorius DH, Hayward I, Jones KL, Stamm E: Sonographic evaluation of pregnancies with maternal varicella infection. J Ultrasound Med 1992; 11:459-463

37. Salzman M, Sood SK: Congenital anomalies resulting from maternal varicella at 25.5 weeks of gestation. Pediatr Infect Dis J 1992; 11:504-505

38. Magliocco AM, Demetrick DJ, Sarnat HB, Hwang W: Varicella embryopathy. Arch Pathol Lab Med 1992; 116:181-186

39. Bale JF, Murph JR: Congenital infections and the nervous system. Pediatr Clin North Am 1992; 39:669-690

40. Isada NB, Paar DP, Johnson MP, et al: In utero diagnosis of congenital varicella zoster virus infection by chorionic villus sampling and polymerase chain reaction. Am J Obstet Gynecol 1991; 165:1727-1730

41. Alexander I: Congenital varicella (Letter). Br Med J 1979; 2:1074

42. Centers for Disease Control (CDC): Increase in rubella and congenital rubella syndrome—United States, 1988-1990. MMWR 1991; 40:1-7

43. Herrmann KL: Available rubella serologic tests. Rev Infect Dis 1985; 7:S108-112

44. Hornstein L, Levy U, Fogel A: Clinical rubella with virus transmission to the fetus in a pregnant woman considered to be immune. N Engl J Med 1988; 319:1415-1416

45. Miller E, Cradock-Watson JE, Pollock TM: Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 1982; 2:781-784

46. Cradock-Watson JE, Ridehalgh MK, Anderson MJ, Pattison JR, Kangro HO: Fetal infection resulting from maternal rubella after the first trimester of pregnancy. J Hyg (London) 1980; 85:381-391

47. Enders G, Nickerl-Pacher U, Miller E, Cradock-Watson JE: Outcome of confirmed periconceptional maternal rubella. Lancet 1988; 1:1445-1447

48. Munro ND, Sheppard S, Smithells RW, Holzel H, Jones G: Temporal relations between maternal rubella and congenital defects. Lancet 1987; 2:201-204

49. Grillner L. Forsgren M, Barr B, Böttiger M, Danielsson L, De Verdier C: Outcome of rubella during pregnancy with special reference to the 17th-24th weeks of gestation. Scand J Infect Dis 1983; 15:321-325

50. Daffos F, Forestier F, Lynch L, Hohlfeld P: Fetal infectious diseases, *In* Harman CR (Ed): Invasive Fetal Tests and Treatment. Cambridge, Mass, Blackwell Publications, in press

51. Levin MJ, Oxman MN, Moore MG, Daniels JB, Scheer K: Diagnosis of congenital rubella in utero. N Engl J Med 1974; 290:1187-1188

52. Alestig K, Bartsch FK, Nilsson LA, Strannegård O: Studies of amniotic fluid in women infected with rubella. J Infect Dis 1974; 129:79-81

53. Cederqvist LL, Zervoudakis IA, Ewool LC, Senterfit LB, Litwin SD: Prenatal diagnosis of congenital rubella. Br Med J (Clin Res) 1977; 276:615

54. Terry GM, Ho Terry L, Warren RC, Rodeck CH, Cohen A, Rees KR: First trimester prenatal diagnosis of congenital rubella: A laboratory investigation. Br Med J (Clin Res) 1986; 292:930-933

55. Cradock-Watson JE, Miller E, Ridehalgh MKS, Terry GM, Ho Terry L: Detection of rubella virus in fetal and placental tissues and in the throats of neonates after serologically confirmed rubella in pregnancy. Prenat Diagn 1989; 9:91-96

56. Eggerding FA, Peters J, Lee RK, Inderlied CB: Detection of rubella virus gene sequences by enzymatic amplification and direct sequencing of amplified DNA. J Clin Microbiol 1991; 29:945-952

57. American Academy of Pediatrics—Committee on Infectious Diseases: Parvovirus, erythema infectiosum, and pregnancy. Pediatrics 1990; 85:131-133

58. CDC: Risks associated with human parvovirus B19 infection. MMWR 1989; 38:81-97

59. Weiner CP, Naides SJ: Fetal survival after human parvovirus B19 infection: Spectrum of intrauterine response in a twin gestation. Am J Perinatol 1992; 9:66-68

60. Porter HJ, Khong TY, Evans MF, Chan VTW, Fleming KA: Parvovirus as a cause of hydrops fetalis: Detection by in situ DNA hydridization. J Clin Pathol 1988; 41:381-383

61. Schwarz TF, Nerlich A, Hottenträger B, et al: Parvovirus B19 infection of the fetus: Histology and in situ hybridization. Am J Clin Pathol 1991; 96:121-126

62. Humphrey W, Magoon M, O'Shaughnessy R: Severe nonimmune hydrops secondary to parvovirus B-19 infection: Spontaneous reversal in utero and survival of a term infant. Obstet Gynecol 1991; 78:900-902

63. Torok TJ, Wang QY, Gary GW, Yang CF, Finch TM, Anderson LJ: Prenatal diagnosis of intrauterine infection with parvovirus B19 by the polymerase chain reaction technique. Clin Infect Dis 1992; 14:149-155

64. Torok TJ: Human parvovirus B19 infection in pregnancy. Pediatr Infect Dis J 1990; 9:772-775

65. Porter HJ, Quantrill AM, Fleming KA: B19 parvovirus infection of myocardial cells (Letter). Lancet 1988; 1:535-536

66. Naides SJ, Weiner CP: Antenatal diagnosis and palliative treatment of non-immune hydrops fetalis secondary to fetal parvovirus B-19 infection. Prenat Diagn 1989; 9:105-114

67. Morey AL, Nicolini U, Welch CR, Economides D, Chamberlain PF, Cohen BJ: Parvovirus B19 infection and transient fetal hydrops (Letter). Lancet 1991; 337:496

68. Pryde PG, Nugent CE, Pridjian G, Barr M, Faix RG: Spontaneous resolution of nonimmune hydrops fetalis secondary to human parvovirus B19 infection. Obstet Gynecol 1992; 79:859-861

69. Gwinn M, Pappaioanou M, George JR, et al: Prevalence of HIV infection in childbearing women in the United States—Surveillance using newborn blood samples. JAMA 1991; 265:1704-1708

70. Berrebi A, Kobuch WE, Puel J, et al: Influence of pregnancy on human immunodeficiency virus disease. Eur J Obstet Gynecol Reprod Biol 1990; 37:211-217

71. European Collaborative Study: Risk factors for mother-to-child transmission of HIV-1. Lancet 1992; 339:1007-1012

72. Hutto C, Parks WP, Shenghan L, et al: A hospital-based prospective study of perinatal infection with human immunodeficiency virus type 1. J Pediatr 1991; 118:347-353

73. European Collaborative Study: Children born to women with HIV-1 infection: Natural history and risk of transmission. Lancet 1991; 337:253-260

74. Mano H, Chermann JC: Fetal human immunodeficiency virus type 1 infection of different organs in the second trimester. AIDS Res Hum Retroviruses 1991; 7:83-88

75. Courgnaud V, Lauré F, Brossard A, et al: Frequent and early in utero HIV-1 infection. AIDS Res Hum Retroviruses 1991; 7:337-341

76. Goedert JJ, Duliege AM, Amos CI, Felton S, Biggar RJ, and the International Registry of HIV-exposed Twins: High risk of HIV-1 infection for first-born twins. Lancet 1991; 338:1471-1475

77. Buta A, Hutton N, Larson E: Immunoglobulins and growth parameters at birth of infants born to HIV seropositive and seronegative women. Am J Public Health 1991; 81:1323-1326

78. Minkoff HL, Henderson C, Mendez H, et al: Pregnancy outcomes among mothers infected with human immunodeficiency virus and uninfected control subjects. Am J Obstet Gynecol 1990; 163:1598-1604

79. Sperling RS, Stratton P: Treatment options for human immunodeficiency virus-infected pregnant women—Obstetric-Gynecologic Working Group of the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Obstet Gynecol 1992; 79:443-448